

GTx-001 Scientific Abstract

Prostate cancer ranks as the second leading cause of cancer deaths among men. The majority of newly diagnosed patients have advanced (stage T3) disease resulting in greater than a 75% mortality rate employing currently available treatments. Novel therapeutics that target the underlying origin of the diseased cells may offer significant advantage at controlling localized cancer. The loss of growth control is central to the majority of malignancies, frequently involving disruption of one of several known tumor suppressor genes. Reactivation of the normal proliferative control mechanisms by introduction of the defective gene may result in destruction or inhibition of the cancer cells. One such gene is p16INK4a which functions as a negative regulator of cell cycle progression through the G1 check point. p16, a cyclin dependent kinase inhibitor (CDKI), specifically inhibits CDKs 4 and 6 from forming complexes with their associated cyclins. This results in another key growth regulatory protein, retinoblastoma (pRb), remaining in a hypophosphorylated state, thus suppressing cellular proliferation. When p16 is absent or mutated, CDK-cyclin complexes actively phosphorylate pRb, enabling progression into S-phase. Frequent alterations of p16 have recently been confirmed in not only prostate cancer cell lines, but also in a large percentage of primary prostate cancer cells. We have developed and characterized an adenoviral vector (type 5 E1/E3 deleted, GTx-001) that efficiently delivers and expresses wildtype p16 in prostate cancer cell lines *in vitro* and *in vivo*. GTx-001 transduced PPC-1, DU-145 and PC3 cells were significantly growth inhibited (51-95%) in comparison to cells transduced with a vector that contained the E.coli β -galactosidase gene (LacZ) in place of p16. Xenografts established with PPC-1 cells that were injected with a single dose of GTx-001 had up to a 67% reduction in tumor volume relative to xenografts injected with LacZ. In addition, mice bearing GTx-001 injected PPC-1 xenografts had a 2.5-fold increase in survival rate in comparison to controls. Hematologic and biochemical values of mice bearing xenograft tumors injected with GTx-001 were equivalent to those of control mice. X-gal staining of xenografts infected with the LacZ-containing virus indicated transduction rates of 95% and suggested a uniform distribution of virus throughout the tumor. Intraprostatic injections of GTx-001 in immunocompetent dogs indicated no viral dissemination into the blood or urine, and minor spread of virus to only the vas deferens and external iliac artery. Finally, PCR analysis of tissues from nude rats receiving orthotopic administration of GTx-001 indicated failure of detectable viral spread. Thus, our preclinical data suggests that adenoviral-mediated replacement of wildtype p16 in prostate cancer cells is a safe and potentially effective therapy.